DOI:
10.1111/ijcp.12917

Document Version
Peer reviewed version

Alpha Blockers in the Management of Ureteric Lithiasis: A Meta-Analysis

Nicholas Raison BSc (Hons), MBBS, MRCS, FHEA[1]

Kamran Ahmed MRCS, PhD[1]

Oliver Brunckhorst BSc (Hons)[2]

Prokar Dasgupta MSc, MD, FRCS Urol, FEBU[1]

Affiliations:

[1]MRC Centre for Transplantation, Division of Transplantation Immunology & Mucosal Biology, Faculty of Life Sciences & Medicine, King's College London, Guy's Hospital, Great Maze Pond, London, SE1 9RT, United Kingdom

[2]GKT School Of Medical Education, King's College London, The Strand, London, WC2R 2LS, United Kingdom

Correspondence to:

Prof. Prokar Dasgupta

Chair of Robotic Surgery & Urological Innovation
MRC Centre for Transplantation, King's College London,
King's Health Partners, St Thomas Street, London SE1 9RT, UK
Ph: +44 (0)20 7188 8580
Fax: +44 (0)20 3312 6787
Email: prokarurol@gmail.com

Word Count: 2470

Key Word: Medical Expulsive Therapy, Alpha Blockers, Ureteric Lithiasis, Renal Colic

ABSTRACT

Introduction

Effective medical expulsion for ureteric stones with α-blockers offers numerous advantages over surgical alternatives. However, its effectiveness remains uncertain and with the publication of new trial data, the available evidence requires reappraisal.

Objective

To assess the efficacy of α-blockers the management of ureteric lithiasis.

Methods

A systematic review of the literature, with pre-defined search criteria, was conducted using Pubmed and Embase. All randomised trials comparing α-blocker monotherapy to placebo or standard therapy were included. Stone expulsion rate was the primary outcome measure. Secondary outcome measures were time to stone expulsion, analgesic usage and pain scores. Subgroup analyses assessed individual adrenergic antagonists and variations in standard therapy. Sensitivity analysis was based on stone location, stone size, Cochrane Risk of Bias score and study protocol. Summary effects were calculated using a random-effects model and presented as Relative risks (RR) and mean differences (MD) for dichotomous and continuous outcome measures respectively.

Results

67 studies randomising 6654 patients were included in the meta-analysis. Stone expulsion rates improved with α-blockers (RR, 1.49; 95% CI 1.38-1.61). Contrast enhanced funnel showed evidence of publication bias. Stone expulsion time was 3.99 days (CI -4.75- -3.23) shorter with α-blockers. Similarly, patients required 106.53mg [CI -148.20- -64.86] less diclofenac compared to control/placebo, and had 0.80 [CI -1.07 – -0.54] fewer pain episodes. Visual Analogue Scores were also reduced, -2.43 [CI -3.87 – -0.99]. All formulations of α-antagonists all demonstrated beneficial effects over conservative treatment/placebo. Sensitivity analysis demonstrated significant effects of stone location, stone size and study design.

Conclusions and Relevance

Despite the opposing results of recently published trial, current evidence continues to demonstrate a potential benefit of α-blocker treatment particularly for distal stones over 5mm.

How did you gather, select and analyze the info you considered in your review?'

Online databases (Medline, Embase) where searched for all studies including abstracts. Clinical trials databases were searched for emerging and unpublished studies. All trials that compared stone expulsion rates in α-blockers and standard therapy or placebo were included in the analysis.

Take-home message for the clinician?

Despite the recent publication of major trials with conflicting results, the results of this meta-analysis continue to support the beneficial role of α-blockers in the management ureteric calculi.

INTRODUCTION

Urolithiasis remains a common complaint in an often otherwise healthy population. With a prevalence of 2-3% and recurrence rates of up to 50%, the morbidity of urolithiasis is clearly reflected in the volume of literature evaluating its management and treatment.

Whilst some stones may remain asymptomatic, an obstructing ureteric calculus with infection represents a surgical emergency requiring immediate intervention. Pain is the main cause for hospital admissions and the likelihood of stone passage is key to determining further management. Smaller stones are liable to pass spontaneously with stones less than 5mm having a 68% chance of passing without treatment.[1] As stone sizes increases, spontaneous passage rates diminish and consequently the need for active treatment increases. Surgical options such as lithotripsy and ureteroscopy offer high stone free rates but at price both in terms of increased costs to the health system and increased risk to the patient. Effective medial expulsive treatment aims to bridge this gap with the potential for treatment of ureteric stone diseased without the risks or costs of surgical interventions.

By inhibiting the contraction of ureteric smooth muscle, α-blockers are believed to promote antegrade stone passage and reduce colic. A large number of randomised studies have been performed assessing their efficacy. Up till now the results from the majority of meta analyses have shown a benefit of alpha blocker treatment in increasing stone expulsion rates and times.[1-6] Medical expulsive therapy is now widely prescribed yet the evidence remains hotly debated[7]. In response the

SUSPEND trial, a large multicentre randomised trial, was conducted assessing the effectiveness of tamsulosin, nifedipine and placebo in treating ureteric calculi.

We have performed the first meta-analysis incorporating these new findings into the existing body of literature to assess the value of α-blockers in treating ureteric calculi.

METHODS

This study was performed using the guidelines set out by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement. PROSPERO registration number: CRD42015029499.

Search Strategy

Searches of electronic databases (Pubmed, Embase) were performed to identify relevant full texts and abstracts. Clinical trial registries (ClinicalTrials.gov; International Clinical Trials Register) were searched for unpublished and emerging trials and authors were contacted for results. Searches were completed on 20th February 2016. No time restrictions were placed on search results. The following MeSH terms and keywords were used in various combinations; “urolithiasis”, “alpha blocker”, “tamsulosin”, “alfuzosin”, “medical expulsive therapy”, “silodosin”, “terazosin”, “doxazosin”, “calculus”, “stone”, “ureteric” “renal colic”, “ureter* colic”, “expulsive therapy”, “facilitated passage”. See supplementary table 1 for the search strategy. Reference lists were searched by hand for further eligible studies.

Inclusion Criteria

All English language studies published up to 20th February 2016 were included if they met the following criteria:

1. Patients presenting with acute ureteric colic
2. Adult patients >18 years
3. Single ureteric calculus
4. A-blocker monotherapy compared to placebo/ standard therapy
5. Prospective, randomised studies

Exclusion Criteria

Studies were excluded if any of the following criteria were met.

1. Studies without original data
2. Studies in which α-blockers were used as adjuvants to lithotripsy or surgery
3. Studies that did not report stone free rates
4. Animal studies

Quality Assessment

All studies were evaluated using The Cochrane Collaboration's tool for assessing risk of bias[8]. Trials were categorised into low, intermediate and high risk groups.

Data Review and Analysis

A standardised data extraction form was agreed prior to the literature searches being performed. Two reviewers independently extracted data using the standardised form. Extracted information included baseline study characteristics (single/multi centre; randomisation method; blinding; power calculation and sample size), number of enrolled patients and drop outs; analysis technique (per protocol/ intention to treat), inclusion/ exclusion criteria, baseline patient characteristics (age, sex), size of stone, position of stone, diagnosis technique, follow up protocol and duration, treatment regime, expulsion rate and time, symptoms, analgesic requirements, adverse effects and withdrawals. Authors of studies for which additional information was required were contacted by email.

Primary analysis compared the rate of stone expulsion in patients receiving standard dose α-blockers to standard therapy or placebo. Standard therapy was defined as symptomatic management regimes including fluids, analgesia, anti-cholinergic agents, anti-spasmodic agents and steroids given to both intervention and control arms.

Secondary analysis compared time to stone expulsion, analgesic usage and pain score variations.

Subgroup analyses, identified a priori, assessed placebo-controlled trials, individual adrenergic antagonists and variations in standard therapy regimes. Unless otherwise stated, all analyses compared α-blockers against conservative treatment/placebo. Sensitivity analysis was performed based on the Cochrane risk of bias score for each study, trial analysis protocol, stone position and stone size.

STATISTICAL METHODS

For dichotomous variables Mantel-Haenszel test pooled risk ratios (RR) were used to evaluate the relative benefit of α-blocker treatment. For continuous variables inverse variance weighted mean differences were calculated. Given the heterogeneity a random effects model was used for both continuous and dichotomous variables. Forest plots were created to display the RR estimates for each study. Potential heterogeneity was assessed using the I^2 statistic and “remove-one” analysis. Publication bias was assessed for by visual inspection of the contrast enhanced funnel plot[9]. Evidence of small study effects was further evaluated using Peter’s test[10]. To further identify possible sources of significant heterogeneity

sensitivity analysis was performed. Analyses were performed using Revman v. 5.3 (Copenhagen: The Nordic Centre, The Cochrane Collaboration) and Stata software v. 14 (Stata Corp, College Station, TX).

RESULTS

The initial search for randomised studies assessing the efficacy of α-blockers resulted in 1184 articles via Medline and Embase. After review of the abstracts, 127 articles were selected for more detailed review. 15 further studies were identified through hand searches of bibliographies. On the criteria detailed above, we excluded 14 studies. Figure 1 provides details of the excluded studies. Finally, 67 studies randomising 6654 patients were selected for inclusion into the meta-analysis (Table 1).

Primary Outcome Analysis

Primary analysis compared α-blocker therapy to standard conservative treatment/ placebo. Random effects analysis assessing the chance of passing a ureteric calculus indicated a RR of 1.49 (95% CI 1.38-1.61) in favour of α-blockers (Figure 2). The I^2 statistic showed significant heterogeneity (I^2 = 75%). Remove-one analysis did not demonstrate a major influence of one particular study. Neither the pooled RR nor I^2 changed significantly with removal of any one study (results not shown). Contour enhanced funnel plot demonstrates significant asymmetry. An absence of studies in the area of low significance suggests a degree of publication bias which was confirmed by Peter's test(P<0.05) (Figure 3). Adjustment of the funnel plot using trim and fill suggested 21 missing studies however these led to only a modest change in outcomes (Supplementary Figure 1). Analysis of estimated effect of this publication

bias showed that whilst pooled RR was reduced to 1.31 (95% CI 1.22 to 1.41), the effects remained significant.

Quality Assessment

Results of quality assessment using the Cochrane Risk of Bias tool can be found in Figure 7. Overall a high degree of bias was seen with only nine studies judged to be at low risk[11-19] whilst 41 were judged to be intermediate risk[20-60] and 17 high risk[61-77]. The most common cause for bias was blinding of both participants and personnel and outcomes assessment.

Secondary Outcome Analysis

The key secondary outcome measure is stone expulsion time. Analysis of 31 studies, 2433 subjects, showed reduced expulsion time with α-blocker therapy by 3.99 days [CI -4.75 - -3.23] compared to standard therapy or control (I^2=88%, p=<0.00001) (Figure 4).

Functional outcomes such as analgesic usage and pain scores were poorly reported by the majority of studies preventing comprehensive analysis. Diclofenac requirements were reported by 13 studies with 909 participants[12,24,25,30,32,37,40,48,52,57,58,66,67]. Alpha-blockers treatment resulted in patients using 106.53mg less diclofenac [CI -148.20 - -64.86] compared to standard therapy/placebo (I^2=99%, p<0·00001).14 studies reported the number of pain episodes experienced within α-blockers and control/placebo

cohorts[12,17,19,24,51,52,57-60,66-68,76]. A-blockers resulted in 0.80 [CI -1.07 – -0.54] fewer pain episodes as compared to control (I^2=81%, p<0.00001). Just six studies, 1130 participants, reported Visual Analogue Scores to pain measurement[16,24,46,51,56,66]. A mean score difference of -2.43 was seen with α-blockers [CI -3.87 – -0.99] (I^2=97%, p<0.00001). 12 studies, 1524 patients, reported side-effects experienced [12,16,21,25,29,48,51,59,65,67,68,76]. A-blockers treatment resulted in a RR of 1.59 [CI 1.01– 2.51] (I^2=0%, p=0·80).

Subgroup analysis all demonstrated similarly beneficial effects to α-blockers treatment. 16 studies of 2633 patients compared α-blockers to placebo[11-16,18-21,32,44,47,64,69,73], RR = 1.28 [CI 1.13-1.44], I^2=81%, p=<0·00001). Confining analysis to just tamsulosin, 48 studies compared it to standard therapy or placebo. Outcomes were very similar to the primary analysis with RR 1·48 [CI 1.35-1.62] in favour of α-blockers (I^2=77%, p=<0.00001). Further studies analysed the individual effects of terazosin, doxazosin, alfuzosin and silodosin. In all cases, treatment with an α-blocker resulted in increased stone expulsion rates (Supplementary Figure 2). Various regimes constituted standard therapy across the 68 studies. Three studies prescribed patients only fluids. 35 studies gave fluids and analgesia and 221 studies gave only analgesia. Seven studies gave all patients anticholinergic medications routinely whilst one study did not stipulate a standard therapy regime[16]. Aside from the three studies that advised fluids alone which demonstrated an equivocal collective outcome, α-blockers were associated with increased stone expansion across all management regimes (Supplementary Figure 3).

Sensitivity analysis was performed to assess for possible sources of heterogeneity.

The effect of bias was explored through comparison of low, intermediate and high risk studies (Figure 7). The nine low risk trials demonstrated a modest but significant benefit of α-blocker therapy (RR 1.15 (CI 1.02- 1.30; I^2 = 77% p=<0.0001). Studies with an intermediate (n=41) or high risk of bias (n=17) showed greater beneficial effects of alpha blockers (intermediate risk RR= 1.52 [CI 1.42-1.62] I^2= 34% p=0.02; high risk RR= 1.60 [CI 1.35-1.91], I^2= 65%, p= 0.0001) (Supplementary Figure 4). The differences between low risk and intermediate risk and low risk and high risk were significant (ratio of relative risk (RRR)= 0.76 [CI 0.66-0.87] and RRR= 0.72 [CI 0.58-0.88] respectively)[78].

Stone location was used to further evaluate the robustness of the data set. The authors' definition of distal, mid and proximal ureteric calculi was followed. The majority of studies included only distal ureteric stones however 10 included proximal stones and four studies included mid ureteric stones. Six studies did not report stone position[35,40,47,72,74,79]. Whilst beneficial in distal and proximal stones, α-blockers were more significantly more effective in treating distal ureteric stones (RR= 1.50 [CI 1.38- 1.62], I^2= 51% p= <0.00001). Effects did not reach significance in mid ureteric stones likely due to the small number of studies included (Supplementary Figure 5).

60 studies reported mean stone size. Stratified by stone size (less or equal to 5mm vs greater than 5mm) both groups showed a higher stone free rate with alpha-blockers vs standard therapy/control (stone ≤ 5mm: RR 1.19 [CI 1.08-1.31], I^2=55% p=0.004; stone > 5mm: RR 1.60 [CI 1.44-1.77] I^2=72%, p<0.00001). As expected, the benefit of α-blocker treatment increased with greater stone diameter (Figure 5).

Sensitivity analysis was also performed on non-adherence to study protocol. Seven studies applied intention to treat analysis[18,33,43,48,58,62,65]. Data for remaining studies, which used either per protocol analysis or did not state an analysis method, were then reassessed using an intention to treat protocol. Primary outcome analysis was largely unaffected (RR= 1.51 [CI= 1.39 -1.65] I^2= 76% p< 0.00001).

DISCUSSION

The pooled results of 67 randomised trials involving 6654 participants suggests that overall α-blockers significantly increase the rate of ureteric stone passage. Use of an α-blocker is associated with a 40% increase in the chance of passing a ureteric stone compared to either standard therapy or placebo. Tamsulosin was used in the majority of studies however all formulations (tamsulosin, doxazosin, terazosin, alfuzosin, silodosin, naftopidil) demonstrated beneficial effects of α-antagonism in stone expulsion. In addition to an increased rate of stone expulsion, α-blockers were associated with a shorter time to stone expulsion.

Variations in outcome measures and study methodologies impeded assessment of secondary outcomes such as pain, analgesic use and side effects. Only nine studies reported diclofenac usage and 11 studies reported pain scores, both of which showed reduce pain with α blocker usage. Conversely, whilst it is acknowledged that side affects are generally poorly reported, a small increased event rate of side effects was seen with α-blockers. Yet treatment appears to be well tolerated. Across

all studies only 21 patients were reported to have withdrawn because of adverse effects.

Significant heterogeneity was demonstrated on analysis. Both the contrast enhanced funnel plot and Peter's test provided evidence for publication bias.

Yet the effects of bias were shown to be more limited and when adjusted for bias, the results remained significant. As seen in previous analysis, whilst publication bias remains fairly prevalent, its impact on outcomes appears to be far more limited[80]. Sensitivity analysis for potential factors of clinical factors proved to be similarly insignificant. In contrast to protocol deviations which did not significantly affect outcomes, an association was seen with overall study quality. Nonetheless even when limited to high quality studies, the beneficial effects of α-blockers remained significant. Stone position and size were also significant factors. A-blockers were significantly more effective in treating stones larger than 5mm with a 38% greater chance of stone passage, likely due to the high spontaneous passage rate of small stones[1]. Stone location influenced treatment efficacy as well. Whereas distal stones were 51% more likely to pass with α-blockers, treatment was ineffective for mid and proximal ureteric stones. A-antagonists target the action of α-adrenoreceptors in ureteral smooth muscle. Most abundant subtypes are 1-a and 1-d particularly in the distal ureter where α-blockers will be most effective. In vitro studies have shown both that α-adrenoceptor stimulation promotes peristaltic activity while antagonism reduces ureteric tone[81-83]. Smooth muscle relaxation leads to reduced intraureteral pressure increasing urine flow above the stone whilst reducing pressure distally. The net increase in the intraureteral pressure gradient results in a

greater expulsive force[84,85]. Inhibition of peristalsis reduces the painful colic associated with stone passage.

In line with previous reviews, this meta-analysis continues to demonstrate a beneficial effect of α-blockers in treating ureterolithiasis[2-6]. These results contrast with the multicentre SUSPEND trial by Pickard et al that did not show a benefit of α-blocker treatment[16]. Variations in clinical factors and study design were found to have significant effects on trial outcomes but these did not affect the review's primary outcome.

Whilst the SUSPEND trial's methodology is in many respects very robust, certain aspects do require further consideration. Although the study included stones less than 10mm, the majority of patients had stones less than 5mm, which have a high chance of passing spontaneously[1]. Subgroup analysis of 282 patients (24.8%) with larger stones (>5mm) was performed showing a trend towards the benefit of tamsulosin over placebo (71.3% vs 60.6%). This did not reach significance but small patient numbers may mean this subgroup analysis was underpowered. Similarly, for stone position a greater but not significant benefit was seen with distal ureteric stones. In contrast our findings for stones over 5mm, based on 3850 patients, demonstrated a significant benefit with α-blockers. Secondly whilst the pragmatic end point of a need for intervention is arguably more useful to the clinician in the field, it is a more imprecise assessment of stone passage rates compared to radiological assessment as used in the majority of studies. Together with a lack of data on compliance rates, there is the potential for under recording stone passages rates especially in the smaller >5mm patient group.

Conclusion

Despite the results of the SUSPEND trial, α-blocker treatment for ureteric stones cannot be conclusively refuted. Particularly in patients with distal stones over 5mm, there is sufficient evidence to support the continued use of medical expulsive therapy with α-blockers.

Acknowledgments

P.D. and K.A. acknowledge educational research support from the Urology Foundation, Olympus and the Royal College of Surgeons of England. P.D. acknowledges support from the Vattikuti Foundation, MRC Centre for Transplantation and NIHR Biomedical Research Centre at King's College London. All other authors declare no conflict of interest.

Contribution

N.R., O.B. and K.A. designed the data extraction form. N.R. and O.B. performed the databases searches, identified eligible studies for inclusion, extracted data and analysed the data. N.R and K.A. drafted and revised the manuscript. P.D. reviewed and revised the manuscript. P.D. is guarantor.

Transparency declaration

The lead, Prokar Dasgupta, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data Sharing

"Technical appendix, statistical code, and dataset available from the lead author, Prof P Dasgupta.

References

1. Preminger GM, Tiselius H-G, Assimos DG, Alken P, Buck C, Gallucci M, et al. 2007 guideline for the management of ureteral calculi. J Urol. 2007 Dec 1;178(6):2418–34.

2. Singh A, Alter HJ, Littlepage A. A systematic review of medical therapy to facilitate passage of ureteral calculi. Ann Emerg Med. 2007 Nov 1;50(5):552–63.

3. Hollingsworth JM, Rogers MAM, Kaufman SR, Bradford TJ, Saint S, Wei JT, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet. 2006 Sep 30;368(9542):1171–9.

4. Seitz C, Liatsikos E, Porpiglia F, Tiselius H-G, Zwergel U. Medical therapy to facilitate the passage of stones: what is the evidence? Eur Urol. 2009 Sep;56(3):455–71.

5. Parsons JK, Hergan LA, Sakamoto K, Lakin C. Efficacy of α-Blockers for the Treatment of Ureteral Stones. J Urol. 2007 Jan 1;177(3):983–7.

6. Campschroer T, Zhu Y, Duijvesz D, Grobbee DE, Lock MTWT. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev. 2014;4:CD008509.

7. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2015 Sep 3.

8. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

9. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol. 2008 Oct;61(10):991–6.

10. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. JAMA. 2006 Feb 8;295(6):676–80.

11. Abdel-Meguid TA, Tayib A, Al-Sayyad A. Tamsulosin to treat uncomplicated distal ureteral calculi: a double blind randomized placebo-controlled trial. Can J Urol. 2010 Jun;17(3):5178–83.

12. Al-Ansari A, Al-Naimi A, Alobaidy A, Assadiq K, Azmi MD, Shokeir AA. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. Urology. 2010 Jan;75(1):4–7.

13. Furyk JS, Chu K, Banks C, Greenslade J, Keijzers G, Thom O, et al. Distal

Ureteric Stones and Tamsulosin: A Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial. Ann Emerg Med. 2016 Jan 1;67(1):86–e2.

14. Hermanns T, Sauermann P, Rufibach K, Frauenfelder T, Sulser T, Strebel RT. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomised, double-blind, placebo-controlled trial. Eur Urol. 2009 Sep;56(3):407–12.

15. Pedro RN, Hinck B, Hendlin K, Feia K, Canales BK, Monga M. Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. J Urol. 2008 Jun;179(6):2244–7–discussion2247.

16. Pickard R, Starr K, MacLennan G, Lam T, Thomas R, Burr J, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. The Lancet. 2015 Jul 24;386(9991):341–9.

17. Sameer, Lal S, Charak KS, Chakravarti S, Kohli S, Ahmad S. Efficacy of nifedipine and alfuzosin in the management of distal ureteric stones: A randomized, controlled study. Indian J Urol. 2014 Oct;30(4):387–91.

18. Sur RL, Shore N, L'Esperance J, Knudsen B, Gupta M, Olsen S, et al. Silodosin to facilitate passage of ureteral stones: a multi-institutional, randomized, double-blinded, placebo-controlled trial. Eur Urol. 2015 May;67(5):959–64.

19. Vincendeau S, Bellissant E, Houlgatte A, Doré B, Bruyere F, Renault A, et al. Tamsulosin hydrochloride vs placebo for management of distal ureteral stones: a multicentric, randomized, double-blind trial. Arch Intern Med. 2010 Dec 13;170(22):2021–7.

20. Agrawal M, Gupta M, Gupta A, Agrawal A, Sarkari A, Lavania P. Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral stones. Urology. 2009 Apr;73(4):706–9.

21. Ahmad H, Azim W, Akmal M, Murtaza B, Mahmood A, Nadim A, et al. Medical Expulsive Treatment Of Distal Ureteral Stone Using Tamsulosin. J Ayub Med Coll Abbottabad. 2015 Jan;27(1):48–50.

22. Aldemir M, Uçgül YE, Kayıgil O. Evaluation of the efficiency of tamsulosin and Rowatinex in patients with distal ureteral stones: a prospective, randomized, controlled study. Int Urol Nephrol. 2011 Mar;43(1):79–83.

23. Arrabal-Martin M, Valle-Diaz de la Guardia F, Arrabal-Polo MA, Palao-Yago F, Mijan-Ortiz JL, Zuluaga-Gomez A. Treatment of ureteral lithiasis with tamsulosin: literature review and meta-analysis. Urol Int. 2010;84(3):254–9.

24. Ayubov B, Arustamov D, Mukhtarov S. 368 Efficacy Of Doxazosin In The Management Of Ureteral Stones. European Urology Supplements. 2007 Jan 1;6(2):114–4.

25. Balci M, Tuncel A, Aydin O, Aslan Y, Guzel O, Toprak U, et al. Tamsulosin versus nifedipin in medical expulsive therapy for distal ureteral stones and the predictive value of Hounsfield unit in stone expulsion. Ren Fail. 2014

Nov;36(10):1541–4.

26. Cervenàkov I, Fillo J, Mardiak J, Kopecný M, Smirala J, Lepies P. Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker--Tamsulosin. Int Urol Nephrol. 2002;34(1):25–9.

27. Cha WH, Choi JD, Kim KH, Seo YJ, Lee K. Comparison and efficacy of low-dose and standard-dose tamsulosin and alfuzosin in medical expulsive therapy for lower ureteral calculi: prospective, randomized, comparative study. Korean J Urol. 2012 Apr 30;53(5):349–54.

28. Chau LH, Tai DCK, Fung BTC, Li JCM, Fan CW, Li MKW. Medical expulsive therapy using alfuzosin for patient presenting with ureteral stone less than 10mm: a prospective randomized controlled trial. Int J Urol. 2011 Jun 30;18(7):510–4.

29. De Sio M, Autorino R, Di Lorenzo G, Damiano R, Giordano D, Cosentino L, et al. Medical expulsive treatment of distal-ureteral stones using tamsulosin: a single-center experience. J Endourol. 2006 Jan;20(1):12–6.

30. Doluoglu OG, Demirbas A, Kilinc MF, Karakan T, Kabar M, Bozkurt S, et al. Can Sexual Intercourse Be an Alternative Therapy for Distal Ureteral Stones? A Prospective, Randomized, Controlled Study. Urology. 2015 Jul;86(1):19–24.

31. Dong KI, Cho WY, Kim TH, Chung JM, Park J, Yoon JH, et al. Effect of Tamsulosin 0.2 mg on the Short-Term Treatment of Urinary Stones: Multicenter, Prospective, Randomized Study. Korean J Urol. 2009;50(6):586.

32. El-Gamal O, El-Bendary M, Ragab M, Rasheed M. Role of combined use of potassium citrate and tamsulosin in the management of uric acid distal ureteral calculi. Urol Res. 2012 Jun;40(3):219–24.

33. Erturhan S, Erbagci A, Yagci F, Celik M, Solakhan M, Sarica K. Comparative evaluation of efficacy of use of tamsulosin and/or tolterodine for medical treatment of distal ureteral stones. Urology. 2007 Apr;69(4):633–6.

34. Ferre RM, Wasielewski JN, Strout TD, Perron AD. Tamsulosin for ureteral stones in the emergency department: a randomized, controlled trial. Ann Emerg Med. 2009 Sep;54(3):432–9–439.e1–2.

35. Georgescu D, Ioniţa-Radu F, Mulţescu R, Draguţescu M, Geavlete B, Geavlete P, et al. The Role Of A1-Blockers In The Medical Expulsive Therapy For Ureteral Calculi - A Prospective Controlled Randomized Study Comparing Tamsulosin And Silodosin. Farmacia. 2014 Jul;63(2):184–8.

36. Ibrahim AK, Mahmood IH, Mahmood NS. Efficacy and safety of tamsulosin vs. alfuzosin as medical expulsive therapy for ureteric stones. Arab Journal of Urology. 2013 May 31;11(2):142–7.

37. Islam MS, Islam MW, Hooda MN, Alam A, Chowdhury GM, Shameem IA. The comparison and efficacy of nifedipine and tamsulosin for the management of lower ureteric stones. Bangladesh Journal of Urology. 2010 Jan;13(1):5–9.

38. Itoh Y, Okada A, Yasui T, Ando R, Tozawa K, Sasaki S, et al. Administration of the selective alpha 1A-adrenoceptor antagonist silodosin facilitates expulsion of size 5-10 mm distal ureteral stones, as compared to control. Int Urol Nephrol. 2013 Jun;45(3):675–8.

39. Itoh Y, Okada A, Yasui T, Hamamoto S, Hirose M, Kojima Y, et al. Efficacy of selective α1A adrenoceptor antagonist silodosin in the medical expulsive therapy for ureteral stones. Int J Urol. 2011 Sep;18(9):672–4.

40. Kaneko T, Matsushima H, Morimoto H, Tsuzaka Y, Homma Y. Efficacy of low dose tamsulosin in medical expulsive therapy for ureteral stones in Japanese male patients: a randomized controlled study. Int J Urol. 2010 May;17(5):462–5.

41. Kim JW, Cho DY, Lee JG. Effect of Tamsulosin on the Expected Treatment of Upper and Lower Ureteral Stones. Korean J Urol. 2007;48(7):724.

42. Küpeli B, Irkilata L, Gürocak S, Tunç L, Kiraç M, Karaoğlan U, et al. Does tamsulosin enhance lower ureteral stone clearance with or without shock wave lithotripsy? Urology. 2004 Dec;64(6):1111–5.

43. Lee SW, Woo SH, Yoo D-S, Park J. Effect of tamsulosin on stone expulsion in proximal ureteral calculi: an open-label randomized controlled trial. Int J Clin Pract. 2014 Feb;68(2):216–21.

44. Maitra T. Prospective randomized trial comparing the efficacy of tamsulosin and tamsulosin combined with nifedepine for the management of lower ureteral stones. Turkish Journal of Urology. 2012.

45. Mohseni MG, Hosseini SR, Alizadeh F. Efficacy of terazosin as a facilitator agent for expulsion of the lower ureteral stones. Saudi Med J. 2006 Jun;27(6):838–40.

46. Mukhtarov S, Turdiev A, Fozilov A, Arustamov D. 774 Using Doxazosin For Distal Ureteral Stone Clearance With Or Without Shock Wave Lithotripsy. Vol. 6. European Urology Supplements; 2007. 1 p.

47. Ochoa-Gómez R, Prieto-Díaz-Chávez E, Trujillo-Hernández B, Vásquez C. Tamsulosin does not have greater efficacy than conventional treatment for distal ureteral stone expulsion in Mexican patients. Urol Res. 2011 Dec;39(6):491–5.

48. Porpiglia F, Vaccino D, Billia M, Renard J, Cracco C, Ghignone G, et al. Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? Eur Urol. 2006 Aug;50(2):339–44.

49. Rathi S, Agarwal A, Patnaik P, Shaw D, Trivedi S. Evaluation of medical expulsive therapy for distal ureteral stone: a prospective randomized controlled study to compare silodosin versus tamsulosin. Vol. 30. Indian Journal of Urology; 2014. 1 p.

50. Reddy RK, Reddy S. The efficacy of alpha-blockers for expulsion of distal

ureteral stones. International Surgery Journal. 2016 Feb;3(I):336–40.

51. Resim S, Ekerbicer H, Ciftci A. Effect of tamsulosin on the number and intensity of ureteral colic in patients with lower ureteral calculus. Int J Urol. 2005 Jul;12(7):615–20.

52. Sayed MA-B, Abolyosr A, Abdalla MA, El-Azab AS. Efficacy of tamsulosin in medical expulsive therapy for distal ureteral calculi. Scand J Urol Nephrol. 2008;42(1):59–62.

53. Taghavi R, Darabi MR, Tavakoli K, Keshvari M. MP03–06: Survey of the effect of tamsulosin and nifedipine on facilitating juxtavesical ureteral stone passage. Vol. 19. Journal of Endourology; 2005. 1 p.

54. Thapa N, Bhandari BB, Hamal BK. Tamsulosin in the management of distal ureteric calculi. Journal of Patan Academy of Health Sciences. 2014 Dec;1(2):19–22.

55. Ukhal MI, Malomuzh OI, Strashny V. Administration of doxazosin for speedy elimination of stones from lower section of ureter. Vol. 35. European Urology; 1999. 3 p.

56. Yencilek F, Erturhan S, Canguven O, Koyuncu H, Erol B, Sarica K. Does tamsulosin change the management of proximally located ureteral stones? Urol Res. 2010 Jun;38(3):195–9.

57. Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. J Urol. 2005 Jun;173(6):2010–2.

58. Yuksel M, Yilmaz S, Tokgoz H, Yalcinkaya S, Baş S, Ipekci T, et al. Efficacy of silodosin in the treatment of distal ureteral stones 4 to 10 mm in diameter. Int J Clin Exp Med. 2015;8(10):19086–92.

59. Ahmed A-FA-M, Al-Sayed A-YS. Tamsulosin versus Alfuzosin in the Treatment of Patients with Distal Ureteral Stones: Prospective, Randomized, Comparative Study. Korean J Urol. 2010 Mar;51(3):193–7.

60. Albert AS, Pillai SR, Mary A, Aravindakshan R. Efficacy of tamsulosin and silodosin as medical expulsive therapy in the management of distal ureteral stones: a randomized controlled study. International Surgery Journal. 2016;3(2):578–81.

61. Alizadeh M, Magsudi M. The effect of tamsulosin in the medical treatment of distal ureteral stones. Glob J Health Sci. 2014;6(7 Spec No):44–8.

62. Autorino R, De Sio M, Damiano R, Di Lorenzo G, Perdonà S, Russo A, et al. The use of tamsulosin in the medical treatment of ureteral calculi: where do we stand? Urol Res. 2005 Dec 1;33(6):460–4.

63. Avdoshin VP, Andriukhin MI, Barabash MI, Taskinen II, Ol'shanskaia EV, Motin PI, et al. [Tamsulosin in the treatment of patients with ureteroliths of the lower third of the ureter clinical and pharmacoeconomic grounds]. Urologiia.

2005 Jan 1;(4):36–9.

64. Bhat SK, Bhushan R, Chakarbarty N. Role of Alfuzosin in Spontaneous Passage of Distal Ureteric Calculi. Journal of Medical Science and Clinical Research. 2015 Nov 1;3(11):8157–60.

65. Said El NO, Wakeel El L, Kamal KM, Reheem Morad El A. Alfuzosin treatment improves the rate and time for stone expulsion in patients with distal uretral stones: a prospective randomized controlled study. Pharmacotherapy. 2015 Apr 30;35(5):470–6.

66. Eryildirim B, Sahin C, Tuncer M, Sabuncu K, Cetinel C, Tarhan F, et al. Effect of medical expulsive therapy on the health-related quality of life of patients with ureteral stones: a critical evaluation. Int Urol Nephrol. 2015 Aug;47(8):1271–5.

67. Griwan MS, Singh SK, Paul H, Pawar DS, Verma M. The efficacy of tamsulosin in lower ureteral calculi. Urol Ann. 2010 May;2(2):63–6.

68. Kumar S, Kurdia KC, Ganesamoni R, Singh SK, Nanjappa B. Randomized controlled trial to compare the safety and efficacy of naftopidil and tamsulosin as medical expulsive therapy in combination with prednisolone for distal ureteral stones. Korean J Urol. 2013 May;54(5):311–5.

69. Laddha A, Mishra S, Ganpule A, Sabnis R, Desai M. Comparison of tadalafil and tamsulosin in medical expulsive therapy for ureteric calculus: prospective, randomized, placebo controlled study. Indian Journal of Urology. 2015 Jan 1;Vol 31(Supplement 1):S39.

70. Liatsikos EN, Katsakiori PF, Assimakopoulos K, Voudoukis T, Kallidonis P, Constantinides C, et al. Doxazosin for the management of distal-ureteral stones. J Endourol. 2007 May;21(5):538–41.

71. Lojanapiwat B, Kochakarn W, Suparatchatpan N, Lertwuttichaikul K. Effectiveness of low-dose and standard-dose tamsulosin in the treatment of distal ureteric stones: a randomized controlled study. J Int Med Res. 2008 May;36(3):529–36.

72. Ramesh O, Rani BS, Prabhu GR. Medical Expulsive Therapy Of Ureteric Calculi-Our Experience. Journal of Evidence Based Medicine and Healthcare. 2015 Oct 5;2(40):2349–562.

73. Su Y-C, Wang C-J, Chen H-W, Tsai P-C. Efficacy of a highly selective α-1 adrenoceptor antagonist in expulsive therapy of distal ureteral stones: A randomized controlled study. Academia Journal of Biotechnology. 2016 Jun 1;4(6):241–6.

74. Sümer A, Kaynar M, Topbaş E, Hassan MA. Comparison of the therapeutic effects of diclofenac sodium, prednisolone and an alpha blocker for the treatment of renal colic. Turkish J …. 2012.

75. Cho JS, Hahn KY, Kwak JM, Kim J, Baek SJ, Shin JW, et al. Virtual reality training improves da Vinci performance: a prospective trial. J Laparoendosc Adv Surg Tech A. 2013 Dec;23(12):992–8.

76. Wang C-J, Huang S-W, Chang C-H. Efficacy of an alpha1 blocker in expulsive therapy of lower ureteral stones. J Endourol. 2008 Jan;22(1):41–6.

77. Zehri AA, Ather MH, Abbas F, Biyabani SR. Preliminary study of efficacy of doxazosin as a medical expulsive therapy of distal ureteric stones in a randomized clinical trial. Urology. 2010 Jun;75(6):1285–8.

78. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ. 2003 Jan 25;326(7382):219.

79. Sun X, He L, Ge W, Lv J. Efficacy of selective alpha1D-blocker naftopidil as medical expulsive therapy for distal ureteral stones. J Urol. 2009 Apr;181(4):1716–20.

80. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ. 2000 Jun 9;320(7249):1574–7.

81. Davenport K, Timoney AG, Keeley FX. A comparative in vitro study to determine the beneficial effect of calcium-channel and alpha(1)-adrenoceptor antagonism on human ureteric activity. BJU Int. 2006 Sep;98(3):651–5.

82. Sasaki S, Tomiyama Y, Kobayashi S, Kojima Y, Kubota Y, Kohri K. Characterization of α1-adrenoceptor subtypes mediating contraction in human isolated ureters. Urology. 2011 Mar;77(3):762.e13–7.

83. Rajpathy J, Aswathaman K, Sinha M, Subramani S, Gopalakrishnan G, Kekre NS. An in vitro study on human ureteric smooth muscle with the alpha1-adrenoceptor subtype blocker, tamsulosin. BJU Int. 2008 Dec;102(11):1743–5.

84. Morita T, Wada I, Suzuki T, Tsuchida S. Characterization of alpha-adrenoceptor subtypes involved in regulation of ureteral fluid transport. Tohoku J Exp Med. 1987 Jun;152(2):111–8.

85. Morita T, Wada I, Saeki H, Tsuchida S, Weiss RM. Ureteral urine transport: changes in bolus volume, peristaltic frequency, intraluminal pressure and volume of flow resulting from autonomic drugs. J Urol. 1987 Jan;137(1):132–5.

Table 1: Included Study Characteristics

Study	Year	Treatment	Number Randomised	Number Analysed	Mean Age (years)	Mean Stone Size (mm)	Stone Expulsion Rate (%)	Stone Expulsion Time (mean days)	Risk of Bias Score
Abdel-Meguid[11]	2010	Tamsulosin 0.4mg vs. Placebo	167	Tamsulosin: 75 Placebo: 75	35	5.5	Tamsulosin: 81.3 Placebo: 56.0	-	Low

Agrawal[20]	2009	Tamsulosin 0.4mg vs. Alfuzosin 10mg vs. Placebo	102	Tamsulosin: 34 Alfuzosin: 34 Placebo: 34	35.1	6.4	Tamsulosin: 82.3 Alfuzosin: 70.5 Placebo: 35.2	Tamsulosin: 12.3 Alfuzosin: 14.5 Placebo: 24.5	Intermediate
Ahmad[21]	2015	Tamsulosin 0.4mg vs. Placebo	100	Tamsulosin: 50 Placebo: 50	36.3	5.8	Tamsulosin: 85.7 Placebo: 54.2	-	Intermediate
Ahmed[59]	2010	Tamsulosin 0.4mg vs. Alfuzosin 10mg vs. Control	90	Tamsulosin: 29 Alfuzosin: 30 Control: 28	40.2	5.3	Tamsulosin: 86.2 Alfuzosin: 76.7 Control: 50.0	Tamsulosin: 7.5 Alfuzosin: 8.3 Control: 13.9	Intermediate
Al-Ansari[12]	2010	Tamsulosin 0.4mg vs. Placebo	100	Tamsulosin: 50 Placebo: 46	36.7	5.96	Tamsulosin: 82.0 Placebo: 61.0	Tamsulosin: 6.4 Placebo: 9.9	Low
Albert[60]	2016	Tamsulosin 0.4mg vs. Silodosin 8mg vs. Control	120	Tamsulosin: 40 Silodosin: 40 Control: 40	33.7	6.9	Tamsulosin: 80.0 Silodosin: 85.0 Control: 37.5	Tamsulosin: 12.0 Silodosin: 12.0 Control: 20.0	Intermediate
Aldemir[22]	2011	Tamsulosin 0.4mg vs. Rowatinex 10mg vs. Control	90	Tamsulosin: 31 Rowatinex: 30 Control: 29	44.1	6.7	Tamsulosin: 80.6 Rowatinex: 43.3 Control: 37.9	Tamsulosin: 3.5 Rowatinex: 6.0 Control: 7.0	Intermediate
Alizadeh[61]	2014	Tamsulosin 0.4mg vs. Control	102	Tamsulosin: 50 Control: 46	-	4.7	Tamsulosin: 82.0 Control: 62.5	Tamsulosin: 3.7 Control: 4.7	High
Arrabal-Martin[23]	2010	Tamsulosin 0.4mg vs Control	70	Tamsulosin: 35 Control: 35	-	-	Tamsulosin: 85.7 Control: 54.3	Tamsulosin: 8.0 Control: 13.8	Intermediate
Autorino[62]	2005	Tamsulosin 0.4mg vs. Control	64	Tamsulosin: 32 Control: 32	44.0	6.1	Tamsulosin: 88.0 Control: 60.0	Tamsulosin: 4.8 Control: 7.4	High
Avdoshin	2005	Tamsulosin 0.4mg vs. Control	87	Tamsulosin: 42 Control: 45	-	7.4	Tamsulosin: 74.0 Control: 24.0	-	High
Ayubov[24]*	2007	Doxazosin 4mg vs. Control	61	Doxazosin:30 Control: 31	-	-	Doxazosin: 93.3 Control: 60.9	-	Intermediate
Balci[25]	2014	Tamsulosin 0.4mg vs. Nifedipine 10mg vs. Control	75	Tamsulosin: 25 Nifedipine: 25 Control: 25	36.8	6.6	Tamsulosin: 76.0 Nifedipine: 64.0 Control: 36.0	Tamsulosin: 9.0 Nifedipine: 9.1 Control: 10.3	Intermediate
Bhat[64]	2015	Alfuzosin 10mg vs. Placebo	92	Alfuzosin: 46 Placebo: 46	-	-	Alfuzosin: 89.1 Placebo: 47.8	-	High
Červenàkov[26]	2002	Tamsulosin 0.4mg vs. Control	104	Tamsulosin: 51 Control: 51	47.0	-	Tamsulosin: 80.4 Control: 62.8	-	Intermediate
Cha[27]	2012	Tamsulosin 0.2mg vs. Tamsulosin 0.4mg vs. Alfuzosin 10mg vs. Control	141	Tamsulosin 0.2mg: 41 Tamsulosin 0.4mg : 30 Alfuzosin: 36 Control: 34	44.1	5.7	Tamsulosin 0.2mg: 78.0 Tamsulosin 0.4mg : 76.7 Alfuzosin: 75.0 Control: 47.1	Tamsulosin 0.2mg: 8.5 Tamsulosin 0.4mg : 7.8 Alfuzosin: 8.2 Control: 13.6	Intermediate
Chau[28]	2011	Alfuzosin 10mg vs. Control	79	Alfuzosin: 33 Control: 34	47.7	6.8	Alfuzosin: 81.8 Control: 50.0	Alfuzosin: 7.1 Control: 8.0	Intermediate
De Sio[29]	2006	Tamsulosin 0.4mg vs. Control	96	Tamsulosin: 50 Control: 46	45.4	6.7	Tamsulosin: 90.0 Control: 58.7	Tamsulosin: 4.4 Control: 7.5	Intermediate
Doluoglu[30]	2015	Tamsulosin 0.4mg vs. Sexual Intercourse vs. Control	75	Tamsulosin: 21 Intercourse: 31 Control: 23	36.1	4.9	Tamsulosin: 81.0 Intercourse: 93.5 Control: 78.3	Tamsulosin: 16.6 Intercourse:10.0 Control: 18.0	Intermediate
Dong[31]	2009	Tamsulosin 0.2mg vs Control	40	Tamsulosin: 19 Control: 21	49.6	4.9	Tamsulosin: 47.4 Control: 38.1	-	Intermediate
El Said[65]	2015	Alfuzosin 10mg vs Control	54	Alfuzosin: 28 Control: 26	32.5	6.1	Alfuzosin: 53.6 Control: 26.9	Alfuzosin: 9.0 Control: 19.0	High

El-Gamal[32]	2012	Tamsulosin 0.4mg vs. Potassium Citrate vs. Tamsulosin 0.4mg and Potassium Citrate vs. Placebo	191	Tamsulosin: 48 PC: 46 Tamsulosin + PC: 46 Placebo: 46	36.5	7.8	Tamsulosin: 68.8 PC: 46.0 Tamsulosin + PC: 85.0 Placebo: 46.0	-	Intermediate
Erturhan[33]	2007	Tamsulosin 0.4mg vs. Tamsulosin 0.4mg + Tolterodine 2mg vs. Tolterodine 2mg vs. Control	120	Tamsulosin: 29 Tamsulosin and Tolterodine: 30 Tolterodine: 28 Placebo: 28	31.5	7.0	Tamsulosin: 73.3 Tamsulosin and Tolt: 70.0 Tolterodine: 46.6 Placebo: 40.0	Tamsulosin: 6.4 Tamsulosin and Tolt: 7.5 Tolterodine: 11.4 Placebo: 12.0	Intermediate
Eryildirim[66]	2015	Tamsulosin 0.4mg vs. Control	120	Tamsulosin: 60 Control: 60	37.2	-	Tamsulosin: 43.0 Control: 36.6	-	High
Ferre[34]	2008	Tamsulosin 0.4mg vs. Control	80	Tamsulosin: 35 Control: 37	46	3.65	Tamsulosin: 71.1 Control: 61.5	Tamsulosin: 1.0 Control: 3.0	Intermediate
Furyk[13]	2016	Tamsulosin 0.4mg vs. Placebo	403	Tamsulosin: 161 Placebo: 155	-	-	Tamsulosin: 87.0 Placebo: 81.9	-	Low
Georgescu[35]	2014	Tamsulosin 0.4mg vs. Silodosin 8mg vs. Control	150	Tamsulosin: 50 Silodosin: 50 Control: 50	44.3	5.17	Tamsulosin: 76.0 Silodosin: 82.0 Control: 50.0	Tamsulosin: 9.0 Silodosin: 7.8 Control: 12.0	Intermediate
Griwan[67]	2010	Tamsulosin 0.4mg vs. Control	60	Tamsulosin: 30 Control: 30	35.1	6.3	Tamsulosin: 90.0 Control: 70.0	-	High
Hermanns[14]	2009	Tamsulosin 0.4mg vs. Placebo	100	Tamsulosin: 45 Placebo: 45	38.5	3.9	Tamsulosin: 86.7 Placebo: 88.9	Tamsulosin: 7.0 Placebo: 10.0	Low
Ibrahim[36]	2013	Tamsulosin 0.4mg vs. Alfuzosin 10mg vs. Control	112	Tamsulosin: 40 Alfuzosin: 40 Control: 32	44.3	5.7	Tamsulosin: 76.0 Alfuzosin: 82.0 Control: 26.0	Tamsulosin: 9.0 Alfuzosin:7.8 Control: 12.0	Intermediate
Islam[37]	2010	Tamsulosin 0.4mg vs. Nifedipine vs. Control	91	Tamsulosin: 32 Nifedipine: 31 Control: 28	45.6	5.9	Tamsulosin: 84.8 Nifedipine: 71.0 Control: 46.4	Tamsulosin: 7.9 Nifedipine: 9.3 Control: 12.8	Intermediate
Itoh[38]	2013	Silodosin 8mg vs. Control	112	Silodosin: 55 Control 56	56.1	-	Silodosin: 72.7 Control: 55.4	Silodosin: 9.29 Control: 13.4	Intermediate
Itoh[39]	2011	Silodosin 8mg vs. Control	187	Silodosin: 89 Control 92	56.9	5.7	Silodosin: 66.3 Control: 50.0	Silodosin: 10.3 Control: 15.2	Intermediate
Kaneko[40]	2010	Tamsulosin 0.2mg vs. Control	71	Tamsulosin: 31 Control: 34	47.5	4.7	Tamsulosin: 77.4 Control: 50.0	Tamsulosin: 15.0 Control: 17.0	Intermediate
Kim[41]	2007	Tamsulosin 0.2mg vs. control	76	Tamsulosin: 34 Control: 42	43.2	5.0	Tamsulosin: 76.5 Control: 42.9	-	Intermediate
Kumar[68]	2013	Tamsulosin 0.4mg vs. Naftopidil 75mg vs. Control	120	Tamsulosin: 40 Naftopidil: 40 Control: 40	33.3	6.9	Tamsulosin: 40.0 Naftopidil: 40.0 Control: 40.0	Tamsulosin: 8.7 Naftopidil: 9.1 Control: 14.0	High
Küpeli[42]	2004	Tamsulosin 0.4mg vs. Control	30	Tamsulosin: 15 Control: 15	42.9	4.8	Tamsulosin: 53.0 Control: 20.0	-	Intermediate
Laddha[69]*	2015	Tamsulosin 0.4mg vs. Placebo vs. Tadalafil	150	Tamsulosin: 50 Placebo: 50	-	-	Tamsulosin: 74.0 Placebo: 58.0	-	High
Lee[43]	2014	Tamsulosin 0.2mg vs. Control	108	Tamsulosin: 54 Control: 54	45.8	-	Tamsulosin: 74.1 Control: 46.3	Tamsulosin: 14.3 Control: 19.6	Intermediate
Liatsikos[70]	2007	Doxasosin 4mg vs. Control	73	Doxasosin: 42 Control: 32	46.2	5.4	Doxasosin: 78.6 Control: 51.6	Doxasosin: 7.3 Control: 10.5	High
Lojanapiwat[71]	2008	Tamsulosin 0.2mg vs. Tamsulosin 0.4mg vs. Control	75	Tamsulosin 0.2mg: 25 Tamsulosin 0.4mg : 25 Control: 25	47.1	6.5	Tamsulosin 0.2mg: 40.0 Tamsulosin 0.4mg : 68.0 Control: 4.0	Tamsulosin 0.2mg: 9.3 Tamsulosin 0.4mg : 10.7 Control: 23.0	High
Maitra[44]	2012	Tamsulosin 0.4mg vs. Nifedipine + Tamsulosin 0.4mg vs. Placebo	150	Tamsulosin: 50 Tamsulosin + Nifedipine: 50 Placebo: 50	36.1	6.5	Tamsulosin: 74.0 Tamsulosin + Nifedipine: 86.0 Placebo: 30.0	Tamsulosin: 28.5 Tamsulosin + Nifedipine: 20.5 Placebo: 37.7	Intermediate
Mohseni[45]	2006	Terazosin 10mg vs. Control	64	Terazosin: 32 Control: 32	41.7	6.8	Terazosin: 90.6 Control: 62.5	Terazosin: 3.2 Control: 6.0	Intermediate
Mukhtarov[46]*	2007	Doxazosin 4mg vs. Control	52	Doxazosin: 27 Control: 25	-	4.1	Doxazosin: 88.9 Control: 72	Doxazosin: 6.4 Control: 8.8	Intermediate

Ochoa-Gomez[47]	2011	Tamsulosin 0.4mg vs. Placebo	71	Tamsulosin: 32 Placebo: 33	38.4	5.3	Tamsulosin: 68.8 Placebo: 69.7	Tamsulosin: 22 Placebo: 23	Intermediate
Pedro[15]	2008	Alfuzosin ? vs. Placebo	69	Alfuzosin: 34 Placebo: 35	39.4	4.0	Alfuzosin: 73.5 Placebo: 77.1	Alfuzosin: 5.3 Placebo: 8.5	Low
Pickard[16]	2015	Tamsulosin 0.4mg vs. Nifedipine 30mg vs. Placebo	1167	Tamsulosin: 378 Nifedipine: 379 Placebo: 379	42.7	4.5	Tamsulosin: 81.2 Nifedipine: 80.2 Placebo: 79.9	Tamsulosin: 16.5 Nifedipine: 16.2 Placebo: 15.9	Low
Porpiglia[48]	2006	Tamsulosin 0.4mg vs.Tamsulosin 0.4mg + Deflazocort vs. Deflazocort vs Control	114	Tamsulosin: 33 Tamsulosin + Def: 33 Def: 24 Control: 24	46.6	5.9	Tamsulosin: 60.0 Tamsulosin + Def: 84.8 Def: 37.5 Control: 33.3	-	Intermediate
Ramesh[72]	2015	Tamsulosin 0.4mg vs. Tamsulosin + Deflazacort vs. Control	90	Tamsulosin: 31 Tamsulosin + Deflazacort: 26 Control: 34	-	-	Tamsulosin: 38.7 Tamsulosin + Deflazacort: 50.0 Control: 32.4	-	HIgh
Rathi[49]*	2014	Tamsulosin 0.4mg vs. Silodosin 8mg vs. Control	87	Tamsulosin: 30 Silodosin: 29 Control: 28	-	-	Tamsulosin: 76.7 Silodosin: 86.2 Control: 50.0	-	Intermediate
Reddy[50]	2016	Tamsulosin 0.4mg vs. Alfuzosin 10mg vs. Placebo	150	Tamsulosin: 50 Alfuzosin: 75 Placebo: 50	26.4	6.7	Tamsulosin: 72 Alfuzosin: 74 Placebo: 32	Tamsulosin: 7.6 Alfuzosin: 8.6 Placebo: 8.6	Intermediate
Resim[51]	2005	Tamsulosin 0.4mg vs. Control	60	Tamsulosin: 30 Control: 30	34.4	7.8	Tamsulosin: 86.6 Control: 73.3	-	Intermediate
Sameer[17]	2014	Nifedipine 30mg vs. Alfuzosin 10mg vs. Control	105	Nifedipine: 35 Alfuzosin: 35 Control: 35	32.2	6.38	Nifedipine: 60.0 Alfuzosin: 85.7 Control: 20.0	Nifedipine: 12.6 Alfuzosin: 12.0 Control: 12.3	Low
Sayed[52]	2008	Tamsulosin 0.4mg vs. Control	90	Tamsulosin: 45 Control: 45	38.2	6.6	Tamsulosin: 88.9 Control: 51.1	Tamsulosin: 7.3 Control: 12.5	Intermediate
Su[73]	2016	Tamsulosin 0.4mg vs. Silodosin 8mg vs. Placebo	204	Tamsulosin: 67 Silodosin: 68 Placebo: 69	51.5	6.6	Tamsulosin: 85.1 Silodosin: 79.2 Placebo: 59.2	Tamsulosin: 6.3 Silodosin: 6.0 Placebo: 9.8	High
Sümer[74]	2012	Alfuzosin 10mg vs. Prednisolone 16mg vs. Control	30	Alfuzosin: 10 Prednisolone: 10 Control: 10	38.0	-	Alfuzosin: 40.0 Prednisolone: 0.0 Control: 0.0	-	High
Sun[79]	2009	Naftopidil 50mg vs. Control	60	Naftopidil: 30 Control: 30	38.0	5.6	Naftopidil: 90.0 Control: 26.7	Naftopidil: 7.0 Control: 6.0	HIgh
Sur[18]	2015	Silodosin 8mg vs. Placebo	246	Silodosin: 119 Placebo: 120	47.0	-	Silodosin: 52.0 Placebo: 44.0	-	Low
Taghavi[53]*	2005	Tamsulosin 0.4mg vs. Nifedipine 20mg vs. Control	64	Tamsulosin: 20 Nifedipine: 20 Control: 24	38.0	-	Tamsulosin: 90.0 Nifedipine: 75.0 Control: 45.83	Tamsulosin: 8.2 Nifedipine: 10.0 Control: 14.2	Intermediate
Thapa[54]	2014	Tamsulosin 0.4mg vs. Control	70	Tamsulosin: 35 Control: 35	31.5	6.3	Tamsulosin: 80.0 Control: 62.9	-	Intermediate
Ukhal[55]*	1999	Doxazosin 2mg vs. Control	65	Doxazosin: 35 Control: 30	-	7.1	Doxazosin: 74.3 Control: 47.0	-	Intermediate
Vincendeau[19]	2010	Tamsulosin 0.4mg vs. Placebo	129	Tamsulosin: 61 Placebo: 61	38.9	3.1	Tamsulosin: 77 Placebo: 70.5	Tamsulosin: 9.6 Placebo: 10.1	Low
Wang[76]	2008	Tamsulosin 0.4mg vs. Terazosin 2mg vs. Control	95	Tamsulosin: 32 Terazosin: 32 Control: 31	50.9	-	Tamsulosin: 81 Terazosin: 78 Control: 55	Tamsulosin: 6.3 Terazosin: 6.3 Control: 10.1	High
Yencilek[56]	2010	Tamsulosin 0.4mg vs. Control	92	Tamsulosin: 42 Control: 50	34.2	6.5	Tamsulosin: 35.7 Control: 30	Tamsulosin: 8.4 Control: 11.6	Intermediate
Yilmaz[57]	2005	Tamsulosin 0.4mg vs. Terazosin 5mg vs. Doxazosin 4mg vs. Control	114	Tamsulosin: 29 Terazosin: 28 Doxazosin: 29 Control: 28	41.5	6.0	Tamsulosin: 79.3 Terazosin: 78.6 Doxazosin: 75.9 Control: 53.6	Tamsulosin: 6.3 Terazosin: 5.8 Doxazosin: 5.9 Control: 10.5	Intermediate
Yuksel[58]	2015	Silodosin 4mg vs. Control	70	Silodosin:35 Control: 35	35.3	6.4	Silodosin: 91.4 Control: 71.4	Silodosin: 8.0 Control: 12.9	Intermediate
Zehri[77]	2010	Doxazosin 2mg vs. Control	66	Doxazosin: 33 Control: 32	33.1	5.39	Doxazosin: 69.7 Control: 37.5	Doxazosin: 7.0 Control: 12.5	High